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Neurologic Complications of Arteriovenous Malformation Embolization Using Liquid Embolic Agents

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BACKGROUND AND PURPOSE: Embolization of arteriovenous malformations (AVMs) is commonly used to achieve nidal volume reduction before microsurgical resection or stereotactic radiosurgery. The purpose of this study was to examine the overall neurologic complication rate in patients undergoing AVM embolization and analyze the factors that may determine increased risk.

MATERIALS AND METHODS: We performed a retrospective review of all patients with brain AVMs embolized at 1 center from 1995 through 2005. Demographics, including age, sex, presenting symptoms, and clinical condition, were recorded. Angiographic factors including maximal nidal size, presence of deep venous drainage, and involvement of eloquent cortex were also recorded. For each embolization session, the agent used, number of pedicles embolized, the percentage of nidal obliteration, and any complications were recorded. Complications were classified as the following: none, non-neurologic (mild), transient neurologic deficit, and permanent nondisabling and permanent disabling deficits. The permanent complications were also classified as ischemic or hemorrhagic. Modified Rankin Scale (mRS) scores were collected pre- and postembolization on all patients. Univariate regression analysis of factors associated with the development of any neurologic complication was performed.

RESULTS: Four hundred eighty-nine embolization procedures were performed in 192 patients. There were 6 Spetzler-Martin grade I (3.1%), 26 grade II (13.5%), 71 grade III (37.0%), 57 grade IV (29.7%), and 32 grade V (16.7%) AVMs. Permanent nondisabling complications occurred in 5 patients (2.6%) and permanent disabling complications or deaths occurred in 3 (1.6%). In addition, there were non-neurologic complications in 4 patients (2.1%) and transient neurologic deficits in 22 (11.5%). Five of the 8 permanent complications (2.6% overall) were ischemic, and 3 of 8 (1.6% overall) were hemorrhagic. Of the 178 patients who were mRS 0–2 pre-embolization, 4 (2.3%) were dependent or dead (mRS >2) at follow-up. Univariate analysis of risk factors for permanent neurologic deficits following embolization showed that basal ganglia location was weakly associated with a new postembolization neurologic deficit.

CONCLUSION: Embolization of brain AVMs can be performed with a high degree of technical success and a low rate of permanent neurologic complications.

The treatment of brain arteriovenous malformations (AVMs) is challenging and often requires the use of all 3 established modalities: superselective embolization, microsurgical resection, and stereotactic radiosurgery. Embolization of AVMs is typically used to reduce nidal size in advance of surgical resection or radiosurgery.[1-8] Embolization can also be used to reduce hemorrhage risk by attempting to eliminate specific areas at high risk for hemorrhage such as intranidal aneurysms,[9] or less commonly, by attempting to completely obliterate the nidus. Recent advances in the embolization technique during the past decade include the development of softer flow-directed microcatheters and the increased use of liquid embolic agents, including cyanoacrylate derivatives to assure nidal penetration during embolization. In addition, superselective provocative testing with barbiturates has been shown to offer an additional level of safety.[10-13]

There is a large multicenter ongoing study to examine the natural history of unruptured AVMs and compare outcomes with multimodality therapy in a randomized fashion (ARUBA study, http://www.arubastudy.org; accessed June 12, 2007). Better understanding of treatment-related complications of embolization would be a key component of understanding risks of therapy versus conservative management, especially for unruptured brain AVMs.[14] Several recent series have reported the complication rates with AVM embolization,[2,5,6,8,15-17] with treatment-related morbidity ranging from 3% to 11%. An embolization protocol using continuous neurophysiologic testing, superselective provocative testing, conscious sedation instead of general anesthesia whenever possible to allow direct clinical examination, staged embolization during several sessions, and strict postprocedure blood pressure control has been adopted at our institution. The purpose of this study was to determine the risk of new neurologic deficits by using this protocol.

Materials and Methods

We performed a retrospective search for all AVM embolizations performed at our institution between January 1, 1995, and December 30, 2005. For each patient, demographics were recorded, including age, sex, date of presentation, presenting symptoms, and history of prior hemorrhages and any prior treatment. Patients with vein of Galen malformations and dural arteriovenous fistulas were excluded. The

angiographic features of each AVM were also recorded, including maximal size, location, presence of deep venous drainage, and involvement of eloquent cortex. These factors were used to arrive at a Spetzler-Martin grade for each AVM. For each embolization session, the number of pedicles embolized, the agents used, and the overall percentage of volume reduction were recorded as well as any complications that occurred during the procedure. Complications were categorized as the following: none, minor non-neurologic complications (such as self-limited groin hematomas), transient neurologic complications (defined as new neurologic deficits that resolved completely within 7 days), permanent nondisabling deficits, and permanent disabling deficits/death. For the patients with permanent deficits, we classified these as either ischemic or hemorrhagic in nature. We also recorded the additional treatment that was performed, including microsurgical resection of part or all of the AVM nidus and radiosurgical therapy.

Embolization Technique

All cooperative patients were treated under conscious sedation. General anesthesia was reserved for pediatric patients or those adults who could not be cooperative with conscious sedation. Continuous electroencephalogram (EEG) and somatosensory evoked potential (SSEP) monitoring were performed in all patients. Standard transfemoral angiographic technique was used to obtain global angiographic images of the internal carotid arteries and vertebral arteries as appropriate. Systemic heparinization was initiated before microcatheter navigation, to achieve an activated clotting time (ACT) 2 to 3 times the normal clotting time. Superselective catheterization was performed by using flow-directed microcatheters of the arterial pedicles supplying the nidus. Following careful analysis of the superselective angiogram, provocative testing was performed for each branch before embolization with an intra-arterial injection of 50-mg sodium amobarbital. An independent neurologist examined all awake patients before and after provocative testing and reviewed the EEG and SSEP findings in all patients. In patients in whom no changes were detected on physical examination or neurophysiologic monitoring, embolization was performed by using either cyanoacrylate derivatives or ethylene-vinyl alcohol copolymer (EVOH). Particulate embolization by using polyvinyl alcohol (PVA) was performed only for rare cases of external carotid branch supply to the pial nidus. All pial branches were embolized by using liquid agents. Detachable or pushable coils were not used in any patients. If necessary, multiple pedicles were embolized at 1 session, with the goal to typically embolize no more than 30%–40% of the nidus in any 1 setting. Postprocedure, heparin therapy was not routinely reversed with the administration of protamine.

All patients were admitted to the intensive care unit for close observation and strict blood pressure control after embolization. The mean arterial pressure was kept typically between 65 and 75 mm Hg for 24–48 hours postembolization. Immediate postprocedure CT was performed in all patients. Patients were also given intravenous corticosteroids before and after embolization and discharged home with a tapering dose for 1–2 weeks. Subsequent embolizations were performed typically at 1- to 2-week intervals.

Statistical Analysis

Univariate analysis was performed to identify risk factors for the presence of any complication (temporary or permanent) by using the following determinants: presenting symptom, maximal nidus size, involvement of eloquent cortex, deep venous drainage, deep location

Table 1: Summary of embolization-related complications

Complication	Per Session (n = 489) (%)	Per Patient (n = 192) (%)
None	451 (92.2)	158 (82.2)
Non-neurologic	5 (1)	4 (2.1)
Transient neurologic deficit	25 (5.1)	22 (11.5)
Permanent deficit, non-disabling	5 (1.0)	5 (2.6)
Permanent deficit, disabling or death	3 (0.6)	3 (1.6)

(basal ganglia/thalamic), Spetzler-Martin grade, pretreatment Modified Rankin Scale (mRS) score, number of embolization sessions, overall nidal volume reduction achieved (across all sessions), and number of pedicles embolized (on a per-session basis). mRS scores were collected on patients before embolization and post-final embolization on all patients.

Results

During the treatment period, 192 patients underwent 489 embolization sessions, with a total of 882 pedicles embolized. There were 99 male (51.6%) and 93 female (48.4%) patients, with a mean age of 32.6 ± 16.1 years. Presenting symptoms were seizure in 70 (36.5%), hemorrhage in 52 (27.1%), focal neurologic deficit in 30 (15.6%), headache in 29 (15.1%), and incidentally discovered AVM in 11 (5.7%). There were 6 grade I, 26 grade II, 71 grade III, 57 grade IV, and 32 grade V patients, separated by Spetzler-Martin grade. Eloquent cortex was involved in 148 (77.1%). Patients underwent a total of 489 embolization sessions, with 48 (25.0%) having 1 session, 58 (30.2%) having 2 sessions, 39 (20.3%) having 3 sessions, and 47 patients (24.5%) having 4 or more sessions of embolization. There were 150 sessions (30.7%) performed in patients who had prior AVM-related hemorrhage, 90 (18.4%) in patients who had prior surgery, 85 (17.4%) in those with prior radiosurgery; 14 sessions (2.9%) were performed within 30 days of AVM-related hemorrhage.

Cyanoacrylate in the form of n-butyl 2-cyanoacrylate (n-BCA) was used in 93.7% of embolizations, EVOH copolymer (Onyx; ev3 Neurovascular, Irvine, Calif) in 4.7% of cases, and a mix of cyanoacrylate and PVA particles in the remaining 1.6% of cases. Mean volume reduction was 63% (range, 5%–95%). When examined by quartiles, 11 patients (5.7%) had 0%–24% mean volume reduction, 51 (26.6%) had 25%–49% reduction, 69 (35.9%) had 50%–74%, and 61 (31.8%) had >75% volume reduction. In addition to embolization, microsurgical resection was performed in 70 patients (36.5%); radiosurgical therapy, in 69 patients (35.9%); both surgery and radiosurgery, in 34 patients (17.7%); and embolization alone at the time of this analysis, in 19 patients (9.9%).

Complications, both per session and per patient, are summarized in Table 1. Of the permanent deficits, 5 of 8 were ischemic (2.6%) and 3 of 8 were hemorrhagic (1.6%). In a univariate analysis, none of the clinical symptoms, AVM characteristics, or embolization results that were examined were found to be statistically significant (Table 2). There was a trend toward a higher rate of new neurologic deficit (temporary or permanent) with AVMs located in the basal ganglia, but this was not statistically significant. Multivariate analysis was not performed because none of the factors met statistical significance in the univariate analysis.

MRS data are summarized in Table 3. There were 171 pa-

Table 2: Results of univariate analysis looking at any complication (transient or permanent neurologic deficit) during embolization*

Criteria	Odds Ratio (95% CI)	P value
Male Gender	0.80 (0.38–1.69)	.56
Presenting Symptom		
Hemorrhage	0.96 (0.42–2.23)	.93
Seizure	0.68 (0.30–1.52)	.35
Headache	0.71 (0.23–2.19)	.55
Neurologic deficit	1.90 (0.76–4.73)	.17
Incidental finding	1.82 (0.46–7.23)	.40
mRS score at diagnosis		
0–2	0.90 (0.28–2.88)	.86
3–5	1.11 (0.35–3.52)	.86
AVM Features		
Eloquent cortex involved	1.48 (0.57–3.84)	.43
Deep venous drainage	1.07 (0.5–2.3)	.86
Spetzler-Martin grade		
I and II	1.50 (0.15–15.46)	.73
III	0.64 (0.07–6.14)	.69
IV	1.09 (0.11–10.35)	.94
V	1.88 (0.19–18.32)	.59
Basal ganglia location	2.11 (0.88–6.10)	.09
Nidal volume reduction (%)		
0–24	0.03 (−0.77–0.83)	.96
25–49	−0.19 (−0.63–0.25)	.65
50–74	−0.19 (−0.59–0.21)	.63
>74	0.35 (−0.04–0.74)	.37
Number of embolization sessions		
1	0.09 (−0.34–0.52)	.82
2	−0.61 (−1.06–0.16)	.18
3	0.23 (−0.22–0.68)	.61
4+	0.31 (−0.11–0.73)	.46
Number of pedicles embolized		
1	−0.33 (−0.68–0.02)	.34
2	0.29 (−0.05–0.63)	.38
3+	0.14 (−0.28–0.56)	.73

Note:—CI indicates confidence interval.
* All data reflect complication rates per patient ($n = 192$), except for number of pedicles embolized, which reflects rates per session ($n = 489$).

Table 3: mRS scores pre- and postembolization

	Pre-embolization		Postembolization	
mRS Score	No.	%	No.	%
0	89	46	94	49
1	57	30	52	27
2	25	13	26	14
3	14	7	14	7
4	2	1	2	1
5	5	3	2	1
6			2	1

tients (89%) who were mRS 0–2 pre-embolization. Postembolization, there were 172 patients (90%) who were mRS 0–2. However, 4 patients (2.3%) who were initially mRS <2 pretreatment were mRS >2 postembolization. Three of these patients had embolization-related complications. One patient underwent 3 sessions of embolization targeting a Spetzler-Martin grade V AVM in the basal ganglia and left hemisphere. After the third embolization, he was unable to undergo further embolization for social reasons. On clinical follow-up, he had gradual progressive neurologic decline such that he was unable to care for himself completely 3 years later.

Discussion

In this series, there were 8 permanent complications (4.2%) with 2.6% nondisabling complications and 1.6% disabling complications or death. Five of these were ischemic (2.6%) and 3 hemorrhagic (1.6%). Our mortality rate was 1.0%, with 2 patients who died from hemorrhage directly related to embolization. The rate of permanent disabling complications or death in this series is somewhat less than those of many of the more recent series. The reasons for this can be multifactorial and can include patient selection, embolic materials, procedural technique, and postprocedure management.

The role of embolization in the management of brain

AVMs has evolved during the past few decades with advances in technology and experience with the technique. Although most AVMs are not curable by using current endovascular techniques, routine embolization of AVMs in several centers is being performed as an adjunct before microsurgical resection or stereotactic radiosurgery. In this application, the risks of embolization must be weighed against the potential benefit.

A large retrospective review summarized the results of embolization in 32 separate series over a 35-year period and divided the data into series pre-1990 and post-1990.[18] The authors found temporary morbidity rates of 10% and permanent morbidity of 8% overall, with 9% permanent morbidity pre-1990 and 8% post-1990. Overall cure by using embolization alone was 4% pre-1990 and 5% post-1990. Mortality was 2% pre-1990 and 1% post-1990. This historic series incorporated a wide range of catheters and embolic agents but is not representative of current embolization technique. There have been several recent large series describing morbidity and mortality with more modern techniques,[2,4,5,8,17] and these are summarized in Table 4.

Hartmann et al[4] evaluated the neurologic outcomes by using mRS scores in 233 patients who underwent 545 embolization sessions between 1991 and 1998. They found that 14% had new neurologic deficits, which is higher than the rate in our series. However their rates of permanent disabling deficits (2%) and treatment-related mortality (1%) are similar to those in this report. The factors that were associated with new deficits in their series included patient age, number of embolization sessions, and the absence of a pretreatment neurologic deficits. They hypothesized that the latter was because the new deficits were more likely to be identified in patients with no pre-existing deficits. They did not find the Spetzler-Martin grade or any specific morphologic features to be predictive of risk for permanent deficit.

Haw et al[5] reviewed the University of Toronto experience with AVM embolization by using almost exclusively liquid embolic agents and found an overall treatment-related incidence of permanent complications of 7.5%, with a 3.9% rate of permanent disabling complications or death in a group of 306 patients undergoing 513 total embolization sessions. In their multivariate analysis, the factors associated with complications included the presence of a high-flow fistula or fistulous component to the nidus, eloquent cortex involvement, or venous glue embolization. This series spanned a long interval from 1984 to 2002, during which time there were significant advances in the technique of AVM embolization, and much of the data are, therefore, more in keeping with a historic series. They did note that there were deaths or disabilities since 1994, when their technique involved using a wedged nidal micro-

Table 4: Treatment-related deficits in recent series of AVM embolization

Series	No. of Patients	No. of Sessions	Permanent Disabling Complication Rate (%)	Notes
Ledezma et al[2]	168	295	6.5	Described as clinically significant complication, not specifically described as temporary or permanent
Hartmann et al[4]	233	545	3	Rate of permanent nondisabling complications not given
Haw et al[5]	306	513	3.9	Eloquence, presence of fistula or venous glue related to complications
Taylor et al[8]	201	339	11	Includes disabling and nondisabling permanent complications; no risk factors for poor outcome found; series mostly used particulate embolization rather than liquid embolic agents.
Current study	192	489	1.6	

catheter position and general anesthesia. In addition, they report that their last postembolization hemorrhage that resulted in disability occurred in 1995.

Ledezma et al[2] reviewed 295 embolization sessions in 168 patients during an 11-year period and found a clinically significant complication rate of 6.5%. Their treatment-related mortality was 1.2%, with 2 deaths directly related to embolization and poor clinical outcome based on the Glasgow Outcome Score in 3%. In their multivariate analysis, they found that periprocedural hemorrhage and a Spetzler-Martin grade of III through IV were predictive of embolization complications.

Taylor et al[8] reported on preoperative embolization in 201 patients undergoing 339 embolization sessions and found an overall 11% per-patient rate of death or permanent deficit. Their rate of permanent deficits is higher than that in our series and those of the other aforementioned recent series. The techniques used by Taylor et al differed from the others because they primarily used PVA particles to achieve embolization, rather than liquid embolic agents. In their series, only 14.8% of the patients were embolized by using liquid embolic agents. In addition, they performed successive embolizations at 2-day intervals, which is more frequent than the embolizations performed in this series. The combination of using particulate rather than liquid agents and more aggressive rapid volume reduction may have contributed to the higher rate of permanent deficits in their series.

In another recent report, Kim et al[17] described the incidence of postembolization neurologic deficits in 153 patients undergoing a total of 203 sessions of embolization. They had 17 permanent deficits, 11 ischemic and 6 hemorrhagic (8.6%), and found that the number of branches embolized was significantly related to new neurologic deficits and that a higher Spetzler-Martin grade, though not statistically significant, was associated with a higher risk of a new deficit. That same trend was not borne out in our univariate analysis, in which Spetzler-Martin grade was not associated with a higher risk of permanent deficit. In addition, neither the number of pedicles embolized per session nor the total number of embolization sessions was associated with a higher rate of complication in our series (Table 2). Their overall complication rate was higher, and they also had fewer embolization sessions per patient: 203 sessions for 153 patients as compared with 489 sessions for 192 patients in our series. The overall risk of ischemic complications was 7.2% in their series and 2.6% in ours. They performed 88% of their procedures with the patient under general anesthesia, precluding provocative testing.[17] All of the cooperative patients in our series were treated by using conscious sedation, which allows us to perform direct physical examination before and after administration of a trial of sodium amobarbital. Provocative testing may afford a greater degree of safety compared with performing embolization with the patient under general anesthesia. Previous work has demonstrated the utility of provocative testing by using sodium amobarbital, as well as the added benefits of performing both neurophysiologic monitoring and clinical examination.[13,19] Provocative testing has also been credited with lowering the permanent complication rate when embolizing Rolandic cortex AVMs.[11]

Another component of our management regimen, which may have reduced postprocedural hemorrhage, was the strict postprocedural blood pressure control, with a goal of minimizing postprocedural hemorrhage. Patients were monitored in the intensive care unit for 24–48 hours postprocedure with a goal of maintaining mean arterial pressures between 65 and 75 mm Hg. The actual parameters were adjusted to take into account each patient's baseline perfusion pressure, the extent of embolization performed, and angiographic features such as slower arterial or venous flow. This strict protocol minimized abrupt postembolization elevations in systolic blood pressure and may have reduced the risk of postembolization hemorrhage. In our series, hemorrhagic complications were seen in 3 patients (1.6%). Heidenreich et al[20] reported 125 interventions in 66 patients, with hemorrhagic complications in 6 patients. Analysis of their data showed that among factors associated with increased risk for hemorrhage were >60% volume reduction and age. In addition, they found that there were significantly better outcomes when patients were managed in a postoperative intensive care unit rather than a medical intensive care unit or stroke unit,[20] which they hypothesized was due to tighter postprocedure blood pressure control.

Conclusion

Embolization of arteriovenous malformations before surgical or radiosurgical treatment can be performed with a high degree of safety and a low rate of permanent neurologic complications. Modern techniques, including the use of flow-directed variable stiffness microcatheters, liquid embolic agents, in conjunction with provocative testing, neurophysiologic monitoring, and strict postprocedure management of blood pressure when possible, may reduce the rate of complications as compared with those in historic series.

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